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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO
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03/07/98 11/25/97 10/11/97

J 370068-9650

EXAMINER

021675 HMD2/0727
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SALES ART UNIT	PAPER NUMBER
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1652

DATE MAILED:

07/27/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on Election 6/14/99

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-25 is/are pending in the application.
Of the above, claim(s) 1-12 is/are withdrawn from consideration.
☐ Claim(s) is/are allowed.
☒ Claim(s) 13-25 is/are rejected.
☐ Claim(s) is/are objected to.
☐ Claim(s) are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☐ received in Application No. (Series Code/Serial Number)
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received:

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s).
☐ Interview Summary, PTO-413
☒ Notice of Draftsperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Art Unit: 1652

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652.

2. Applicant's election with traverse of Group III in Paper No. 7 is acknowledged. The traversal is on the ground(s) that claims of Group I & III are inherently dependent upon the type of the enzyme which comprise the chimeric enzyme, in that the function of the enzyme in the chimeric enzyme limits the way in which the chimeric enzyme is used. This is not found persuasive because the function of the chimeric enzyme is not limited to by the enzyme activity in a method for the determination of the analytes (Group III) but is also modulated upon binding of a binding molecule to the mimotope (Group I). Applicants further argue that it would be reasonable that a search of the claims of Group I, encompassing the chimeric enzyme will also necessarily gather art related to the nucleic acids encoding those enzymes (Group II). However, this is not found persuasive. The reasons for restricting the enzyme and the nucleic acid (DNA) are because they are chemically and biologically distinct molecules. Additionally, the DNA has other functions besides encoding the enzyme. Since the beta-lactamase and the DNA are biologically and chemically distinct, the manner of using the DNA may not necessarily involve the enzyme. The enzyme and DNA have fundamentally different molecular structure, each with its own set of functionality. Enzyme, for example is biologically active, whereas DNA encoding the enzyme, is not. Also it may be noted that searching the data base for a chimeric enzyme does not always lead to the corresponding DNA art.

The requirement is still deemed proper and is therefore made FINAL.

Art Unit: 1652

3. Claims 13-25 are under consideration in this examination, not 14-24 as previously indicated. Claims 1-12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

4. The Draftsman's objection(s) to the drawings is enclosed here in the notice on form PTO-948. Correction is required.

5. *Sequence Rules*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. See the enclosed notice to comply.

Tables 1-6 & 8-9 of this application present amino acid sequences. Also in pages 29-30, 32, 37-38 & 40 of the specification, short nucleotide sequences are disclosed. According to 37 CFR 1.821-825, every disclosed amino acid sequence of four or more residues or nucleotide sequence of 10 or more must be identified by a SEQ ID NO. Specifically, Rule 1.822(e) requires the use of three letter abbreviation for amino acids. Applicants must alter these Tables, provide a new version of the sequence listing and disk, or petition for an exception to these rules.

6. Claim 18 is objected to because of the following informalities: Claim 18 depends from a later claim 19, which is incorrect. A dependent claim may only depend from a prior claim. Applicants may have intended claim 18 to depend from claim 13. Appropriate correction is required.

Art Unit: 1652

7. Claims 13 & 20 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13 & 20 depend from claim 1, which has been restricted and withdrawn from consideration. Correction as indicated is required.

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Claims 13-25 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method of determining the amount of an analyte in a test sample using a chimeric β -lactamase as the starting enzyme, and comprising six amino acids insert in the loop of the rim of the active site residues 103-105, for example; or the alpha. 11 helix residues 271-272 of the R-Tem β -lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66. The claims are broader than the enablement provided by the disclosure with regard to the exceedingly large number of known enzymes that cannot be used as a starting enzyme, given the guidance of a single chimeric β -lactamase to produce other chimeric enzymes that can be modulated upon binding, to any binding molecule or mimotope. Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) [*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]]. The Wands factors are: (a) the quantity of experimentation

Art Unit: 1652

necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The claims are directed to a method for determining the presence of an analyte in a test sample using any enzyme as the starting enzyme, modifying the enzyme(s) to create a functional or enzymatically active chimeric enzyme having a binding site moiety, to which a binding molecule can attach. From the guidelines provided for construction of chimeric β -lactamase and the skill of the artisan in the area of molecular biological and enzymology it would have been possible to make a number of single, double or multiple amino acid(s) modifications in the chimeric β -lactamase structure in order to selectively modify the catalytic sites, to enable modulation upon binding. However, the transfer of such a construct to any amino acid modification within the β -lactamase enzyme or any other enzyme in order to first produce a chimeric enzyme and further attempt to selectively insert or replace single, double or multiple amino acid inserts and develop chimeric enzyme binding site moiety which can successfully attach itself to a binding molecules, lacks adequate guidance, is unpredictable and would result in undue experimentation. It lacks adequate guidance because the chimeric insertion developed for β -lactamase or the specific amino acid modifications made in order to develop the binding molecule to achieve the desired attachment to the molecule, is not a matter of routine. This is because the same insertions/replacements of amino acid(s) in the β -lactamase amino acid chain, to

Art Unit: 1652

other enzyme may not necessarily result in producing an active chimeric enzyme because there is no information about the sequence homology or functional similarity among different enzymes and the art of amino acid modification is highly unpredictable. Thus, the specification fails to provide guidance to other enzymes, other than β -lactamase and at the specific positions, that can be successfully utilized in effectively creating chimeric enzymes and the appropriate steps required for such constructs. In the absence of information regarding homologies and similarities between the exemplified enzyme and those from other groups, it remains unpredictable as to whether the disclosure concerning the instant β -lactamase can be used to develop a method for determining analytes using other chimeric enzyme (Claim 13) binding site moiety which can successfully attach itself to any binding molecules (claims 14-19), or where the analyte and substrate contact the enzyme simultaneously or in steps (claims 20-25), or where the test sample contains the analyte (claim 25). Therefore, the skilled artisan would require guidance, such as the number and presence of other chimeric enzymes as well as appropriate techniques for identifying the active catalytic and binding sites and the effect(s) chimeric insertions/replacements or modifications and information on sequence homology or functional similarity among different enzymes, in order to make and use chimeric enzymes in a manner commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

10. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1652

Claim 18 recites the limitation "said analyte" in claim 19. There is insufficient antecedent basis for this limitation in the claim.

11. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is vague and grammatically incorrect in the 'contacted with the chimeric first'. The suggested change would be to use the phrase 'contacted first with the chimeric enzyme' instead, or other suitable modification will overcome this rejection.

12. Claims 13 & 20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are:

The claimed method is for determining the presence and amount of an analyte, which lacks a control step without the chimeric enzyme, which would be required for eliminating the background signal and for determining the actual amount of the analyte in the test sample. Suggested step 4 for claim 13; or step 3 for claim 20 : 'detecting the amount of catalysis of the substrate compared to a control without the enzyme....'. Suggested or other suitable modifications will overcome this rejection.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Art Unit: 1652

Claim 13-14, 16-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Rodrigues et al. [Cancer Research 55 : 63-70, 1995]. Rodrigues et al. teach a method for the construction of humanized anti-p185^{HER2} antibody . The antibody is useful as a building block to engineer a disulfide linked Fv (dsFv) β -lactamase fusion (or chimeric) protein for use in antibody-dependent enzyme mediated prodrug therapy. The variant enzyme is modulated upon binding the target antigen (see abstract & page 63 column 2 & page 64, Fig 2). Applicants definition of mimotope (page 2, lines 17-22) is the preferred BSM (binding site moiety) (claim 13, step 2) and a BSM is engineered into the target molecule by site directed mutagenesis (Page 64, Fig. 2) and the fusion protein then attaches to the antibody (or binding molecule). The specification defines 'analyte' as an antibody (page 21, lines 1-2). The fusion protein retains both antigen-binding plus kinetic activity (claim 13, step 3) (see abstract) in murine serum (test sample of claim 1, step 1). The reference therefore identifies the three steps outlined in claim 13 or the two steps of claim 20, as explained above. The claims are written so broadly as to be anticipated by the reference.

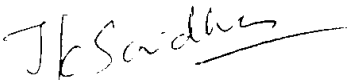
14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15am to 4:45pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Tekchand Saidha
Art Unit 1652
July 26, 1999


Tekchand Saidha
Patent Examiner